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Treflan (trifluralin (a,a,a-trifluoro-1,6-dinitro-1,6-diphenyl-p-toluidine)).
0.05 ppm trifluralin in or on whole, washed carrots.
0.01 ppm trifluralin in or on, whole unwashed cantaloupes and cucumbers.

PETITION PENDING NO. 7F-0555

Elanco Products Company
Division of Eli Lilly & Co.
Indianapolis, Indiana
(AP 3-677)

Availability data of Treflan in support of the safety of a temporary tolerance
at 0.05 ppm in or on sugar beets, Pesticide Petition No. 63-0494 was
submitted in May 26, 1956 memorandum.

The following evaluation is of the completed long term studies referred
to in the May 26, 1968 memorandum, some completed and the remainder in an
interim status at that time.

Water rat feeding study: Petitioner's Study No. 131-81.

Groups of Hazelton strain rats, 5 of each sex were fed 0, 10, 200, 2000
and 20,000 ppm Treflan diets for 1 years.

Observations for effects included:

1. Growth
2. Mortality
3. Food intake
4. Food efficiency utilization
5. Hemograms including leukocytes, hemoglobin and erythrocyte counts.
6. Necropsy to search for compound related gross organ and tissue
effects.
7. Microscopic examination of skeletal muscle, heart, lungs, liver,
spleen, pancreas, salivary gland, thymus, thyroid, adrenal,
adrenocortical lymph node, GL tract and genitourinary system.

Results:

Groups consuming the 20,000 ppm treflan diets were affected as
evidenced by decreased growth, food intake and food utilization. Slight
local bile duct proliferation was recorded in one of the 20,000 ppm
rats that the petitioner relates to compound ingestion.

Effects were absent in the other diet groups. Two thousand ppm was

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as illustrated on a no-effect level.

Petitioner's rat feeding study No. R-02-03: Groups of Cox strain albino rats, 25 of each sex, were fed 0, 200, 1000 and 2000 ppm Treflan diets for two years.

Observations for effects included:

1. Weekly weights.
2. Food consumption.
3. Macroscopy of surviving animals.
4. Hematology at experiment termination of all survivors included hematocrits, hemoglobin, erythrocyte and leukocyte counts, leukocyte differential counts and prothrombin time.
5. Blood glucose and SGOT was measured in about $\frac{1}{4}$ of the survivors.
6. Weights of liver, kidneys, heart, spleen, thyroid, adrenals, prostate and reproductive organs were determined.
7. Microscopic examination of sections of heart, lung, liver, spleen, thymus, GI tract, genitourinary system, testes, gland, adrenals and thyroid from surviving rats.

No compound related influences were noted revealed by the observations made. These data demonstrate that can tolerate 2000 ppm Treflan diets for two years without effects.

Treflan dog studies: Petitioner's study No. 31-61: Groups of mongrel dogs, 1 of each sex were orally dosed 7 days a week at 2.5, 5 and 25 mg/kg enter for ten years. Two females were similarly dosed at 10 mg/kg for two years.

Detailed observations including behavior, body weight, blood studies, urinary function, organ weights, biochemical tests, gross and microscopic organ and tissue examination did not reveal compound related influences.

A female on 10 mg/kg was bred to a male on 25 mg/kg at the 17th month. Gestation was normal and 6 healthy pups were born; 3 survived to weaning.

Petitioner's study No. 31-19-62: Groups of purchased beagle dogs were orally dosed 0 mg/kg (1 of each sex), 1 mg/kg (2 of each sex), 2.5 mg/kg (2 of each sex), 5 mg/kg (2 males) and 10 mg/kg (2 males) with Treflan for one year.

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Observations and effects paralleled those made for the mongrel dog study. Effects were not revealed by observations made.

Petitioner's dog (study No. 3-24-66) Groups of purebred beagle dogs were orally administered 0.6 mg/kg (♂ at each sex), 10 mg/kg (♀ of each sex) and 20 mg/kg (♀ of each sex) of rosin for three years.

Observations for effects were similar to those in the other dog studies.

Compound related changes in the 10 mg/kg group were described as occasional emesis and a trend toward heavier livers.

Lipochromic pigment found in the livers of the rosin treated dogs was deemed not significant by the investigators. Disregarding the liver lipochromic pigment, 400 ppm can be judged as the no effect level in this study.

Justification for not considering the pigment as an effect, is based on this pigment being found in dogs livers without known cause, this pigment not associated with degenerative liver changes in the test dogs, this pigment not being found in the livers of the dogs in the two other long term feeding experiments and the lack of evidence of liver damage in rats fed 2000 ppm diets for two years.

The data demonstrates dogs can be dosed orally with 10 mg/kg of rosin for three years without effect.

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April 19, 1987

as breeding experience. Petitioner's dog study [21-62] After approximately two years on the experiment each female was bred to a male within her group.

Dose ppm Fe	Schedule	Number pups born			Number pups weaned
		M	F	U	
1.4	C	3	6	3	6
172	C	1	4	1	4
170	C	3	2	3	2
1000 ppm					
720 ppm	400 ppm	4	2	4	2
10 " " /kg	400 ppm	2	3	0	0
45	400 ppm	2	1	2	1
170 ppm	1000 ppm	2	1	2	1
	1000 ppm	2	1	2	1
	1000 ppm	2	1	2	1

Contribution studies:

21-62 Groups of 10 each strain rats, 6 males and 12 females per group were fed 0, 200 and 1000 ppm Freelan diets in a 4-generation (2 litters each) reproduction study.

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Fertility Study Indexes

F₀ Generation

Index	Fertility	Mortality	Mobility	Inflation
Letter	a	b	c	d
0	63	100	94	13
200	75	100	98	92
2000	53	72	100	77

F₁ Generation

0	20	96	40	26	100	27	100	56
200	61	61	98	97	91	92	26	93
2000	69	57	100	100	71	76	95	99

F₂ Generation

0	77	83	100	68	93	35	77	13	90
200	75	75	91	100	69	96	73	96	
2000	0	20	0	94	0	31	0	100	

F₃ Generation

0	59	92	100	100	83	67	93	67
200	100	100	95	97	87	99	93	88
2000	100(F ₂)	100(F ₂)	100	100	93	100	100	92

Total

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April 19, 1957

F₁ Littermate or-continuous Breeding

Indices	Fertility	Pregnancy	Viability	Lactation
1st year				
9	7.3	75.1	77.1	89.1
200	64.2	94.0	90.7	85.1
2000	69.2	92.6	78.3	83.8

Appropriate average of 8 litters each per female

Number of percent rate recommended

Indices	1st	2nd	3rd	4th
original 0 ppm	6	3	12	4
25 ppm	8	3	12	12
50 ppm	1	2	-	11
100 ppm	-	2	7.5	6
200 ppm	4	6	6	6
400 ppm	-	6	6	3

stillbirths

Indices	%	No. litters	No. still b.	No. litters	No. still b.	N.L	N.SB
1st year litter	23	23	21	13	22	11	
2nd litter	2	6	22	6	16	0	
3rd litter	16	15	17	9	2	11	
4th litter	15	0	22	11	2	0	
Original Parents continuous breeding	51	65	62	37	54	33	

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April 19, 1967

Microscopic examination of skeletal muscle, heart, lungs, liver, spleen, pancreas, salivary gland, thymus, thyroid, adrenal, lymph node, utricle and genitourinary system of the parents of the offspring did not reveal compound related effects.

Organ/tissue weights for all liver, kidneys, testes, adrenals and uterine reproductive system of the parent rats did not reveal compound influences.

This data demonstrated reproduction performance was uninfluenced during production of 4 generations with a 200 ppm trellan diet. The 2000 ppm diet was without influence for production of approximately 3 continuous litters in the original parent group.

Two female animals were bred in the 2000 ppm group for production of the third and fourth generation for a valid conclusion of possible effects. The loss of a valuable female was related to environmental conditions. The particular related an episode of moving the experimental rats when the ♀, females were pregnant for their second litter. As a consequence, only one 2000 ppm female was available for breeding for the fourth generation.

The matron described a change of quarters involving a 20 mile move, followed by extreme inconsistency in housing temperatures due to heating system malfunction during severe winter weather.

Lactation Uterotology Study: Groups of lactating New Zealand White does were fed selected Trellan from the 8th thru the 16th day of pregnancy.

Treatment	No. pregnant	Viable pups	Fetal pups	Resorption sites
Control	7	49	2	13
2000 ppm	7	47	2	2
3000 ppm	6	65	6	1
4000 ppm	7	73	15	24

In the 16th day of gestation the does were killed, fetuses removed and examined for viability and malformation and implantation sites were counted.

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April 10, 1967

Visible signs of fetal malformation were not found except for 2 fetuses from one 225 mg/kg doe. Their appearance was described as underdeveloped hind legs and hind quarters. Four normal fetuses were part of the same litter.

The increased number of visible young and increased number of abortions seen in the 1000 mg/kg groups could not be related to the administered compound. Assuming they are related to compound effects, 100 mg/kg can be assigned as the no-effect level.

Summary of investigations - no-effect levels:

2000 ppm, 2 year rat feeding studies.

200 ppm, 4 generation rat reproduction study.

1000 ppm, cow/calf breeding, approximately 10 litters from each female.

150 ppm, two, 2 year dog feeding studies.

100 ppm, one, three year dog feeding study.

100 ppm, dog breeding study.

100 mg/kg-rabbit teratology study.

CONCLUSION:

The partition data supports the safety of the requested residue tolerances.

INVESTIGATOR:

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File Number: 4-19-67

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